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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/362,286	07/27/1999	ANUPAMA K. NADKARNI	CPI-099	6674

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EXAMINER	
MURPHY, JOSEPH F	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 04/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/362,286	NADKARNI ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 43-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *44-59* is/are allowed.

6)☒ Claim(s) *1-14,43 and 60-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Claims 1-14 and 43-66 are pending and under consideration.

Response to Amendment

The rejection of claims 1-14, 43-59 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, has been obviated by Applicant's amendment and is thus withdrawn.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14, 43 stand rejected, and new claims 60-66 are rejected, under 35 U.S.C 112, first paragraph, because the specification, while being enabling for a mutant IL8 receptor and a mutant galanin receptor, does not reasonably provide enablement for any other mutant mammalian G protein coupled receptor, for reasons of record set forth in the Office Action of 6/12/2002 and 4/4/2003. There is not adequate guidance as to the nature of the mutant mammalian G protein coupled receptor which Applicants claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with this claim.

The rejected claims encompass mutant mammalian GPCRs that differ from a wild-type GPCR by comprising a 4 amino acid stretch closer to the C-terminal end than the N-terminal end. Claims 1-14, 43 as written encompass mutants of any and all GPCRs, and the new claims, 60-66, encompass mutants of somatostatin type I receptors, somatostatin type II receptors, somatostatin type III receptors, nociceptin receptor, galanin receptors and IL-8 receptors. The specification discloses mutants if the galanin and IL-8 receptors. The rejection of record set forth that the unpredictability of the protein art is shown in Bowie et al (Science, 1990, 247:1306-1310) which teaches that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). Additionally, Yan et al. teaches that in certain cases, a change of only two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another (Yan et al., Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. *Science* 290: 523-527, 2000). It is also known in the art that a single amino acid change in a protein's

sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). Additionally, the Gether reference is cited to further show the unpredictability of structure to function determinations in the GPCR superfamily. Gether teaches that GPCRs do not share any overall sequence homology. The only structural feature common to all GPCRs is the presence of seven transmembrane-spanning α-helical segments connected by alternating intracellular and extracellular loops, with the amino terminus located on the extracellular side and the carboxy terminus on the intracellular side (page 91, column 1, second paragraph). The three major subfamilies of GPCR's include the receptors related to the "light receptor" rhodopsin and the β 2 -adrenergic receptor (family A), the receptors related to the glucagon receptor (family B), and the receptors related to the metabotropic neurotransmitter receptors (family C) (page 91, column 1, second paragraph). The overall homology among all type A receptors is low and restricted to a number of highly conserved key residues The high degree of conservation among these key residues suggests that they have an essential role for either the structural or functional integrity of the receptors (page 91, column 1, third paragraph). Family B receptors include approximately 20 different receptors for a variety of peptide hormones and neuropeptides, such as vasoactive intestinal peptide (VIP), calcitonin, PTH, and glucagon (page 92, Fig. 1). Except for the disulfide bridge connecting the second (ECL 2) and third extracellular loops (ECL 3), family B

receptors do not contain any of the structural features characterizing family A receptors (page 91, column 2, second paragraph). Family C receptors have, like family A and B receptors, two putative disulfide-forming cysteines in ECL 2 and ECL 3, respectively, but otherwise they do not share any conserved residues with family A and B receptors (page 92, Fig. 1 and page 91, column 2, third paragraph). The Gether reference thus teaches that the GPCR superfamily is large and diverse, and that residues necessary for function are not shared between families, and even within families, residues critical for function are not known. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Since the claims encompass variant polypeptides and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention. There is no guidance provided in the specification as to how one of ordinary skill in the art would generate a mutant GPCR polypeptide other than those exemplified in the specification. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue.

Applicant argues that it would be routine for one of ordinary skill in the art to generate a mutant GPCR containing a mutation in the X1X2X3X4 motif, which causes increased signaling as compared to the wild-type GPCR. Applicant further argues that the instant invention teaches of members of the family of chemotactic cytokines, which have been proposed to be named "chemokines" for short, are being identified as vital initiators and promulgators of inflammatory and immunological reactions. Applicant further argues that the chemokines of the present invention are categorized, according to Gether, in the subfamily A, also known as the

Rhodopsin/βz adrenergic receptor-like (see Gether, 2000, page 91-92). Applicant further asserts that these teachings constitute a blue print that enables the skilled artisan to practice the invention across a wide range of mutant GPCRs containing a mutation in the X1X2X3X4 motif without undue experimentation. However, claims 1-14, 43 under rejection are not limited to any particular GPCR, but encompass all GPCRs of any type, and claims 60-66 encompass other types of GPCRs not exemplified in the Specification, and as demonstrated in the references, the amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's function from mere sequence data are limited. Given the large and diverse nature of the GPCR superfamily, and the lack of conservation of residues or motifs across the families, one of skill in the art would need to make each and every possible mutant GPCR and test for enhanced function, since there is no direction provided in the specification as to which of the residues or motifs are critical for the enhanced activity, and whether this motif is conserved across the entire superfamily of GPCR's. Since detailed information regarding the structural and functional requirements of the proteins are lacking, it is unpredictable as to which variations meet the limitations of the claims for enhanced activity. In the instant case there are a large number of mutant GPCR's which would meet the structural limitations of the claims, but one of skill in the art would need to make each and every possible mutant GPCR and test for enhanced function, since there is no direction provided in the specification as to which of the residues or motifs are critical for the enhanced activity, and whether this motif is conserved across the entire superfamily of GPCR's, while only a few examples are provided.

Therefore, given the breadth of claims 1-14, 43, 60-66 and based upon the evidence presented in the Bowie et al. reference showing that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex, the Yan et al. and Voet et al. references which demonstrates that the change of only one or two amino acids can radically alter protein function, and the Gether reference which teaches that the GPCR superfamily is large and diverse, and that residues necessary for function are not shared between families, and even within families, residues critical for function are not known, and absent sufficient evidence to the contrary, a preponderance of the evidence demonstrates that it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claims 1-14, 43 stand rejected, and new claims 60-66 are rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record set forth in Paper No. 19, 6/12/2002. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The rejected claims encompass mutant mammalian GPCRs that differ from a wild-type GPCR by comprising a 4 amino acid stretch closer to the C-terminal end than the N-terminal

end. Claims 1-14, 43 as written encompass mutants of any and all GPCRs, and the new claims, 60-66, encompass mutants of somatostatin type I receptors, somatostatin type II receptors, somatostatin type III receptors, nociceptin receptor, galanin receptors and IL-8 receptors. The specification discloses mutants if the galanin and IL-8 receptors. Applicant argues that there is sufficient written description in Applicants' specification regarding the claimed molecules, to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed, as required by section 112, first paragraph. Applicant further argues that the claimed genus of the mutant GPCRS of the present invention is defined by structural features that are described in the specification, recited in the claims, and commonly possessed by its members. In particular, the structure of the claimed genus, i.e., the structure of the mutant GPCR, the corresponding the amino acid motif (XlX2X3X4) and the position of the point mutation within the amino acid motifs (see page 7, line 17 through page 8, line 40 of the specification) is specifically taught in the specification. Furthermore, the instant specification teaches distinguishing structural features within the claimed genus, including putative membrane spanning domains.

However, claims 1-14, 43 under rejection are not limited to any particular GPCR, but encompass all GPCRs of any type, and claims 60-66 encompass other types of GPCRs not exemplified in the Specification. As set forth *supra*, the protein art is unpredictable based upon the evidence presented in the Bowie et al. reference showing that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex, the Yan et al. and Voet et al. references which demonstrates that the change of only one or two amino acids can radically alter

protein function and the Gether reference which teaches that the GPCR superfamily is large and diverse, and that residues necessary for function are not shared between families, and even within families, residues critical for function are not known. Applicant has disclosed a mutant IL8 receptor and a mutant galanin receptor, but has not described a polypeptide comprising a functional mutation of any and all other GPCRs. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides used in the claimed method. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed: there is no guidance in the art as to what the defining characteristics of the polypeptides might be. Thus, applicant was not in possession of the claimed genus.

Claims 60-66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification as originally filed does not provide support for the invention as now claimed: a mutant mammalian G protein coupled receptor wherein the wild type receptor the wild type G protein-coupled receptor selected from the group consisting of somatostatin receptor type 1, somatostatin receptor type II, somatostatin receptor type III, and human nociceptin receptor.

Applicant's amendment, submitted 11/4/2003, does not provide sufficient direction for the written description for the above mentioned limitations of claims 60-66. The specification originally discloses the IL-8 and galanin receptors. The specification as filed does not provide a written description or set forth the metes and bounds of this phrase. The specification does not provide direction for the instant sequence encompassing the above-mentioned "limitations" as they are currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office action

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above.

Conclusion

Claims 1-14, 43, 60-66 are rejected.

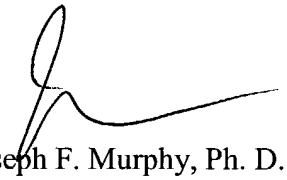
Claims 44-59 are allowable.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571) 272-0871.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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Patent Examiner
Art Unit 1646
April 13, 2004